PROSPECTIVE SCIENTIFIC REVIEW OF NCI INTRAMURAL CLINICAL TRIALS

1. THE NCI PROTOCOL REVIEW & MONITORING COMMITTEE (PRMC)

   - The PRMC was chartered to provide prospective, scientific review of NCI intramural clinical trials and to identify high priority clinical trials. The formation of a separate committee to perform scientific review stems from a recommendation of the NCI Intramural Review Committee and a mandate from the NIH.
   - The PRMC is constituted of senior investigators representing most of the Branches of the Center for Cancer Research (CCR) as well as members from the Division of Cancer Epidemiology and Genetics (DCEG), the Cancer Therapy Evaluation Program (CTEP), and the Office of the Director, CCR. Committee members terms are not time-limited. Attachment 1 is a roster of current committee members and their affiliation.
   - The PRMC will meet monthly on the third Tuesday of the month from 10:00 AM until 12:00 PM in the Surgery Branch Conference Room (Bldg. 10, Rm. 2S235).

2. CCR RESEARCH PRIORITIES

   Mission

   - Foster interdisciplinary research to control or eliminate cancer
   - Facilitate translational and clinical research
   - Expedite technology development
   - Enhance training, particularly in interdisciplinary and translational research
   - Build partnerships within NCI and with other NIH Institutes, Federal agencies, extramural academia, biotechnology companies, and the pharmaceutical industry

   Clinical Mission

   - Conduct concept-based (science-driven) clinical trials that evaluate new therapies rather than testing existing ones
   - Discover and develop molecularly targeted agents and combinations of agents for use in clinical trials
   - Develop novel approaches to early cancer detection and prevention
   - Develop and deliver novel technologies for molecular diagnosis of cancer
   - Emphasize understudied diseases and cancers with increasing incidence or involving special populations
   - Develop better preclinical models and methods to expedite development of novel interventions for cancer

CCR – An Environment for Interdisciplinary, Translational Research

- Close link between basic clinical, genetic and epidemiologic research in a comprehensive and interactive interdisciplinary environment
- Collaborative environment for scientists to foster the development of emerging technologies and approaches for the enhancement of patient care
- Long-range commitment of resources
- Availability of the NIH Clinical Center, which contains more than 50% of the NIH-funded general clinical research center beds in the U.S.
- Recruitment, training, and retention of clinical and basic science fellows in multidisciplinary research
- Complement government, academic, and industry research efforts

3. THE PROTOCOL REVIEW PROCESS

- Scientific review of all new protocols will be completed by the PRMC before submission for review by the NCI IRB.
- In performing the scientific review of new protocols the PRMC will consider:
  - the quality, originality, and importance of the scientific hypothesis with an emphasis on trials that incorporate a mechanistic hypothesis and include laboratory correlates or new technologies;
  - the scientific and statistical validity of the trial design;
  - the resources required to complete the trial; and
  - the relationship of the trial to other trials within and outside the NIH to avoid inappropriate duplication.
- Principal Investigators (PI's) have the option of submitting their proposed trial as a concept (using a concept sheet developed by the PRMC - Attachment 2) or as a full protocol, although the concept review can not substitute for review of the full protocol. The concept proposal and the full protocol should receive Lab/Branch review and approval prior to submission to the PRMC.
- Thirty copies of the concept sheet or full protocol should be submitted to the PRMC two weeks prior to the scheduled meeting. The informed consent form should **not** be submitted to the PRMC.
- A cover memo, which is signed by the PI and Branch Chief, should describe
  - how the protocol fulfills the CCR clinical research mission (see above),
  - whether adequate resources are available to conduct and monitor the trial,
  - the rationale for including other centers if this is a multi-institutional trial,

  - that the protocol has been reviewed and approved by the Branch. The PI may elect to submit a written copy of the Branch review with a point-by-point response to Branch review, but this is not required by the PRMC.

- Protocols, such as eligibility screening protocols, which are not science-based but fulfill important Lab/Branch functions, are eligible for expedited review by the PRMC Chair.
- Multi-institutional or cooperative group protocols that originate from a CCR investigator (i.e., the CCR investigator is the lead PI on the protocol) must be reviewed and approved by the PRMC before distribution to and review by the participating institutions, cooperative group, or CTEP.
- Each protocol or concept submitted for review will have PRMC members assigned as primary and secondary reviewers prior to the meeting. These reviewers will summarize the protocol and lead the discussion of the protocol at the meeting.
- *Concept Review*: The review at the concept stage allows the PI to receive feedback and comments from the PRMC before writing a full protocol. The PRMC will not approve/disapprove concept sheets. The PI will receive an indication of the overall priority that PRMC places on the proposed clinical trial and comments from the committee members describing how the trial could be improved. The full protocol must subsequently be reviewed by the entire committee at a regular monthly meeting, as if it were a new submission. The PI should submit a cover memo that specifically addresses the PRMC's comments on the concept sheet with the full protocol.
- *Protocol Review*: The protocol should follow the CCR standardized protocol format (available at http://home.ccr.cancer.gov/IRB/forms.html) or the CTEP format for CTEP sponsored trials (templates can be downloaded from http://ctep.info.nih.gov/forms/index.html) and receive Lab/Branch review and approval prior to submission to the PRMC. The protocol PI and AIs will not be present for the review, and any PRMC member who is a PI or AI on a protocol under review will recuse themselves from the discussion. An exception will be made for the PRMC chair and statisticians if they are an AI on a protocol. The PRMC will
  - approve the protocol without stipulations,
  - approve with stipulations (and determine if the PI response and revised protocol will be reviewed by the full PRMC, the primary reviewers or the PRMC chair prior to IRB submission), or
  - disapprove the protocol.

  A written ballot will be used to record each members vote. The PRMC decision, stipulations, recommendations, and comments from the CC Pharmacy Department will be transmitted to the PI in the form of PRMC minutes. The

minutes will be transmitted to the PI via e-mail one week after the meeting. For protocols approved with stipulations, the PI must respond to each stipulation and describe the changes made to the protocol in a cover memo that is submitted with the underlined changes made to the protocol, the revised protocol and a copy of the PRMC minutes prior to final approval of the protocol. For protocols that are disapproved, the PI may elect to respond to the PRMC's comments, in which case the protocol will be re-reviewed by the full committee after it has been re-reviewed and approved by the Branch.

- *Amendments*: The PRMC will only review protocol amendments which substantially alter the trial design, statistical section, or convert a trial from a single institution to a multi-institution trial or at the NCI IRB's request. Amendments may receive expedited review by the PRMC Chair at the discretion of the PRMC Chair.
- After final approval by the PRMC, the protocol can be submitted for IRB review and CTEP/sponsor review.

4. COORDINATION OF THE PROTOCOL REVIEW PROCESS

- The requirement for formal protocol review for scientific content by the PRMC requires close coordination of all components of the review process to avoid long delays in opening protocols.
- PRMC and IRB records and activities will coordinated out of the same office using same protocol file.
- The IRB chair is an *ad hoc* member of PRMC.
- An attempt will be made by the PRMC and the IRB to minimize the lead time for protocol submission and the turn around time to provide the PI with a written comments from the respective committees. The PRMC meeting is scheduled two weeks before the IRB submission deadline for new protocols.
- The NCI IRB will focus on issues related to the protection of human subjects and the informed consent procedure, whereas the PRMC will focus on scientific review. The PRMC will not review informed consents (an informed consent should not be submitted to the PRMC with the protocol).

Attachment 1: Protocol Review and Monitoring Committee Roster

MEMBER	AFFILIATION	EXPERTISE
Paul Albert	Biometric Research Branch, DCTD	Statistics
Frank Balis (Chair)	Acting Clinical Director	Pediatric oncology & clinical pharmacology
Susan Bates	Cancer Therapeutics Branch	Drug resistance & drug development
Kevin Camphausen	Radiation Oncology Branch	Radiation therapy
William Dahut	MOCRU (GU/GYN Research Unit)	Prostate cancer & drug development
Howard A Fine	Neuro-Oncology Branch	Brain tumors & angiogenesis
Dan Fowler	Experimental Transplantation & Immunology Branch	Transplantation & immunology
Mark H. Greene	Clinical Genetics Branch, DCEG	Epidemiology & genetics
Anthony Murgo	Investigational Drug Branch, CTEP	Drug development & clinical pharmacology
John Janik (*ad hoc*)	IRB Chair	
Liz Jones	Department of Radiology, CC	Imaging
Kenneth H Kraemer	Basic Research Laboratory	DNA repair & dermatology
Lance A Liotta	Laboratory of Pathology	Proteomics
Steven Rosenberg	Surgery Branch	Surgery, immunotherapy & tumor vaccines
Seth Steinberg	Biostatistics & Data Management Section	Statistics
Mark Udey	Dermatology Branch	Immunology
Lyuba Varticovski	Center for Cancer Research	Translational research
Brigitte Widemann	Pediatric Oncology Branch	Drug development & neurofibromatosis
Wyndham Wilson	MOCRU (Lymphoma Research Unit)	Lymphoid malignancies
Robert Yarchoan	HIV & AIDS Malignancies Branch	HIV & Kaposi's sarcoma

Attachment 2: Protocol Concept Sheet

Information required by the PRMC for a protocol concept review is listed below. The format for submitting this information is shown on the following page. PLEASE BE BRIEF. Ideally each protocol concept sheet should not exceed two pages.

Demographic Information:

Protocol title

Principal Investigator

Lab/Branch performing the trial

Collaborating Investigators/Institutions - *from within and outside the NCI*

Projected duration of the trial

Projected accrual ceiling and expected accrual rate (no. of patients per year)

IND Holder - *for investigational agents*

Category of trial - *select from the following:*

Primary treatment - specify phase (e.g., phase I, phase II, phase III, pilot)

Supportive care - list primary treatment protocols from which patients are accrued

Non-therapeutic - specify type (e.g., tissue procurement, natural history, long-term follow-up, normal volunteer)

Background/Relevance of Trial:

Summarize hypothesis/rationale and supporting data. Describe relevance of this trial to overall mission of Lab/Branch.

Include information about related or similar intramural and extramural trials. (Does the proposed protocol complement or compete with other ongoing trials.) Stress original/unique aspects of protocol. (Why should it be performed at the NCI?)

Study Objectives/Endpoints:

Summarize the objectives and endpoints of the trial.

Trial Design:

Summarize briefly or attach a schema of the trial. Provide statistical justification for design and projected patient accrual.

Laboratory Correlates:

Describe any laboratory studies resulting from specimens (e.g., serum, tumor/tissue biopsies) obtained from patients treated on the trial

Designate whether this concept sheet should be circulated to other Labs/Branches to identify groups that may be interested in collaborating in this study.

Resource Consumption:

List Division resources, including research nurses and data managers, required to complete the trial. Patient care resources covered under the Management Fund should not be included.

Comments:

Additional information critical to the review (e.g., importance of protocol to training program, relationship to other Lab/Branch studies).

Attachment 2 (Cont.): Protocol Concept Sheet Format

Protocol Title:

P. I.: **Branch/Lab:**

Collaborating Institutions:

Accrual Ceiling: **Accrual Rate:** **Trial Duration:**
IND Holder: **Category:**
Background/Relevance:

Study Objectives/Endpoints:

Trial Design:

Laboratory Correlates:

Resource Consumption:
Comments: